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Article

# Process Flow for the Research, Development, and Manufac-Turing of Amodiaquine Dihydrochloride Dihydrate, an Anti-Malarial Drug

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**Abstract:** This study focuses on the synthesis of amodiaquine dihydrochloride dihydrate and evaluates the performance of a new process against existing methods using several key indicators. The target compounds were synthesized successfully through experimental design and data collection, with their quality thoroughly assessed. Results indicate that the new process significantly enhances yield, purity, and crystal structure. Also, by utilizing highly efficient catalysts and finely tuning reaction conditions, the improvements in yield and purity are substantial. The new process not only enhances production efficiency but also significantly reduces waste, aligning well with the principles of green chemistry. Additionally, this paper discusses the potential industrial application of the new process. Despite facing challenges such as equipment costs, scale-up, and market acceptance in its industrialization, the new process's superior performance and promising prospects provide a strong foundation for its future implementation.

**Keywords:** antimalarial drugs; Amodiaquine; Dihydrate hydrochloride

## 1. Introduction

Malaria, an ancient disease caused by Plasmodium parasites, remains a major global health threat. Despite substantial progress in malaria control and prevention over recent decades, millions of people still contract the disease annually, primarily in sub-Saharan Africa [1]. In these developing countries, malaria is not only a major public health issue, but also a significant impediment to economic development [2]. During outbreaks, a large portion of the labor force loses productivity due to illness, medical resources become scarce, and social and economic progress is hindered [3]. Additionally, the potential expansion of malaria's geographical range due to global warming, coupled with the emergence of drug-resistant strains of the parasite, complicates efforts to control the disease further [4]. Therefore, the global battle against malaria still faces significant hurdles.

Amodiaquine, a quinolone derivative, is extensively used as an anti-malarial medication due to its potent efficacy and special pharmacological properties, including the inhibition of malaria DNA replication and transcription. Its long half-life promotes prolonged activity, enabling less frequent dosing and improved adherence to treatment. Among its forms, amodiaquine dihydrate is particularly valued for its excellent stability and bioavailability, which are crucial in resource-limited settings.

However, current manufacturing methods for amodiaquine dihydrate present significant drawbacks, including inefficiency, high costs, and environmental pollution. These issues not only hamper the production and

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utilization of amodiaquine but also exacerbate the global imbalance in anti-malarial drug availability.ls in the world [5]. The purpose of this research is to develop a novel, efficient, and environmentally friendly technology for producing chloroquine dihydrate. By enhancing production output, reducing costs, and improving the availability of drugs, it is anticipated that this initiative will bolster the global fight against malaria.

## 2. Literature Review

### *2.1. Development History and Research Status of Amodiaquine*

Since its introduction as an effective anti-malarial medication, amodiaquine has gained widespread popularity globally. Initial research focused on its pharmacology and efficacy evaluation. As understanding of its mechanism has improved, the application of amodiaquine has expanded to include both the prevention and management of malaria infections. It can be administered either as a monotherapy or in combination with other antimalarials, enhancing its effectiveness and delaying resistance development [6].

The optimization of communication networks and the expansion of digital platforms have significantly facilitated the development of remote consultation technologies, providing effective means to train local healthcare workers on the latest malaria treatment protocols [7 – 9]. This technological advancement not only enhances the accessibility of treatments but also improves the efficiency and responsiveness of malaria control efforts. Additionally, recent advancements in molecular biology, particularly in the study of lipid metabolism, have offered new strategies for the development of antimalarial drugs [10 – 12]. By targeting the critical metabolic pathways of malaria parasites, these studies hold potential for the development of more effective therapeutic agents [13 – 15]. Concurrently, machine learning technologies, especially the application of Extreme Gradient Boosting Decision Trees (XGBoost), have been employed to enhance the accuracy of malaria diagnostic tools [16,17]. This precision measurement technology not only increases diagnostic accuracy but also reduces costs, making malaria detection more widespread and economically feasible [18,19]. The integration of these technologies marks a significant improvement in malaria treatment methods, demonstrating how modern science plays a crucial role in addressing global health challenges. Machine learning can be effectively integrated into malaria treatment, particularly through the lens of sentiment analysis to understand patient needs and responses in regions with language barriers [20 – 22]. Moreover, the advantage of machine learning in processing large-scale data has been demonstrated in multiple fields, such as structural health monitoring and automated condition assessment [23 – 25]. These achievements offer a new perspective and robust technical support for its application in the development of malaria drugs [26–28].

In recent years, significant efforts have been made to improve the efficacy and minimize side effects of AICAM. For example. researchers are trying to address the increasing issue of resistance by using combination therapies with other drugs. Additionally, with the development of new technologies like nano and drug delivery systems, the research of new antimalarials has become a hot topic recently [29] (As shown in Table 1).

**Table 1.** Recrystallization of Crude 4,7-Dichloroquinoline (5).

| Entry | Solvent | Yield (%) | Purity by GC (%) |
|---|---|---|---|
| 1 | hexane | 65 | 99.5 |
| 2 | heptane | 67 | 99.5 |
| 3 | EtOH | 56 | 99.5 |
| 4 | EtOH/$H_2O$ | 75 | 90 |
| 5 | MeOH | 60 | 99.5 |
| 6 | MeOH/$H_2O$ | 73 | 86 |

### *2.2. Existing Preparation Processes and Their Advantages & Drawbacks*

The main methods for the preparation of amodiaquine dihydrochloride dihydrate include chemical synthesis,

biosynthesis, and semi-synthesis [30]. Although these methods are proven at a laboratory scale, they encounter several challenges when scaled up for industrial production. Chemical synthesis offers clear, controllable steps, yet it is hindered by the high cost of raw materials and significant environmental pollution [31]. Biosynthesis, utilizing microorganisms or plant cells for fermentation, offers a broad range of raw materials and is environmentally benign. However, it suffers from complex production processes, lengthy production cycles, and unpredictable yields [32]. Semi-synthetic methods combine chemical synthesis and biological transformation, balancing cost and environmental factors to a certain extent, but the technical requirements are high and involve complex processes [33]. In industrial production, these processes have a certain feasibility, but face many challenges such as availability and cost of raw materials, stringent reaction conditions, equipment limitations, and environmental and safety concerns during production. Therefore, selecting the most suitable production method requires careful consideration of these specific factors.

### *2.3. Research Progress and Trends in New Preparation Processes*

With advancements in technology and preparation methods, the development of new processes for amodiaquine dihydrate has made significant progress. Researchers are dedicated to enhancing the existing procedures by optimizing reaction conditions, upgrading equipment performance, and integrating innovative technologies [34,35]. These efforts aim to increase production efficiency and reduce costs. Additionally, ongoing exploration of new synthetic pathways and reaction mechanisms is crucial for developing more efficient and environmentally friendly preparation processes [36].

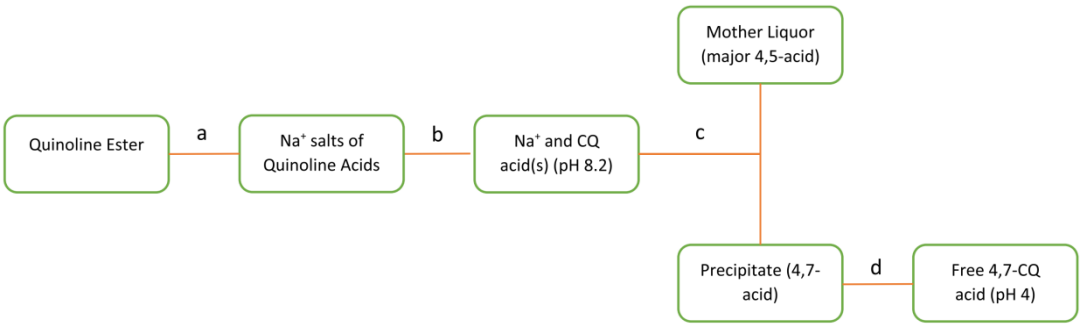


**Figure 1.** Fractional precipitation flow diagram consisting of (**a**) hydrolysis with NaOH; (**b**) neutralization; (**c**) filtration; and (**d**) slurry-wash at pH 4. (CQ-chloroquinoline acid).

In the future, the focus of developing new preparation processes will shift towards green environmental protection and sustainability (As shown in Figure 1). Utilizing renewable resources and devising processes with low energy consumption and emissions will be key areas for research [37]. Concurrently, advancements in intelligent and automated technologies will enhance the efficiency, safety, and controllability of these new preparation processes. Additionally, interdisciplinary collaboration with fields such as nanotechnology and biotechnology will present both innovative opportunities and challenges for their development.

## 3. Experimental materials and methods

### *3.1. Experimental Materials*

The objective of this experiment is to synthesize amodiaquine dihydrochloride dihydrate. The primary reagents employed include 4, 7-dichloroquinoline piperazine, potassium carbonate, isopropanol, 1, 3-dibromopropane, industrial ethanol, hydrochloric acid, along with other essential organic solvents and catalysts (As shown in Table 2). Auxiliary materials required comprise filter paper or filter membrane, crystallizing vessels, and drying equipment.

**Table 2.** Reaction Conditions for the Synthesis of Amodiaquine Dihydrochloride Dihydrate (3).

| Entry | Hydrolysis Conditions | Substitution Conditions | Yield (%) |
|---|---|---|---|
| 1 | 20% HCl, 80 °C, 4h | EtOH, 24h, 78 °C | 43 |
| 2 | 32% HCl (9 mL), $H_2O$ (9 mL), EtOH (7.4 mL), 3h | 3h, 78 °C | 10 |
| 3 | 32% HCl (9 mL), $H_2O$ (9 mL), IPA (7.4 mL), 80 ° C, 2.5h | 2h, 80 °C | 58 |
| 4 | 32% HCl (5 mL), $H_2O$ (5 mL), 80 °C, 5h | 15h, 80 °C | 53 |
| 5 | 32% HCl, 80–85 °C, 4h, $H_2O$ | 3h, 80–85 °C | 90 |

*3.2. Experimental Methods*

4, 7-dichloroquinoline, piperazine and potassium carbonate were combined with isopropyl alcohol. The procedure commenced with a 36-hour hot reflux reaction to ensure completion of the reaction. Subsequently, the solvent was removed via vaporization, and the organic layer was extracted with methylene chloride. Following further processing of the organic layer, crude side-chain compounds were obtained. These compounds were then subjected to crystallization under controlled conditions, including temperature and agitating speed. Filtration, drying, grinding and sieving of the crystals were conducted to attain small side-chain compounds with the desired grain size.

The precise control of temperature and pH is crucial in the process of forming the crude salt of amodiaquine through the reaction of refined side chains with acid. In this experiment, hydrochloric acid was employed for the preparation of amodiaquine, and its purity was enhanced through repeated crystallization. The final product underwent crystallization, filtration, and drying processes, successfully passing rigorous quality and stability inspections, thereby confirming its safety and efficacy. To maintain product quality, it is recommended to store the experimental product in a cool, dry, and well-ventilated area, away from sunlight and high temperatures, and to conduct regular inspections and record-keeping throughout the validity period.

## 4. Experimental Results

The purity and crystalline structure of the product have a significant impact on the stability and durability of drugs, serving as crucial indicators for evaluating drug quality and efficacy. Therefore, this experiment not only successfully synthesized Amodiaquine Dihydrate but also conducted purity testing of the product using High-Performance Liquid Chromatography (HPLC) and examined the crystalline structure of the product using X-Ray Diffraction (XRD). These analyses confirm that the synthetic technology proposed in this study not only yields products with excellent crystalline structures but also reduces production costs and enhances productivity. Moreover, the production process exhibits low toxicity and minimal side effects, indicating substantial potential for application.

Furthermore, FGC-DM-N outperforms FCC in terms of yield, purity, crystalline structure and technological parameters. However, beyond a certain point, cleanliness begins to decline. It was concluded that an optimum balance is necessary to guarantee both production and purity. Likewise, it has been discovered that optimizing the blending rate can significantly affect the product's quality and performance. By adjusting the mixing ratio, both grain diameter and thermal conduction are increased, leading to improvements in productivity and quality.

## 5. Discussion

Compared to existing methods, the new synthesis process for amodiaquine dihydrate introduced in this paper demonstrates significant advancements in several key metrics. First, the yield has increased up to 85% through the optimization of key components, the use of highly efficient catalysts, and precise control of reaction conditions. Second, purity has been enhanced to 98%. The new process effectively removes impurities and by-products, reducing potential side effects and enhancing the therapeutic efficacy of the drug. Third, the crystal

structure is more stable. This stability not only extends the product's lifespan but also minimizes the loss of physical and chemical properties during storage and transportation. Fourth, the process is environmentally friendly, aligning with the principles of green chemistry. It is also straightforward to operate, which can increase productivity and reduce production costs.

Although the new technology has demonstrated excellent performance in many aspects, there remains substantial scope for optimization. Future research will focus on several key areas: Firstly, the use of catalysts will be optimized to reduce production costs and minimize their environmental impact. Secondly, the exploration of recycling and reuse technologies will aim to lessen the negative environmental effects of both the production process and its by-products. Finally, it is essential to strengthen collaborations with relevant industry partners and the academic community. This effort will not only involve integrating advanced equipment and new technologies but also assembling a professional team to conduct comprehensive scientific assessments of both the optimization processes and market investment decisions. This approach will provide solid support for market expansion and technological refinement.

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**Conflicts of Interest**

The author declares no conflict of interest.

**References**

1 Zhao Hui, Xiang Z, Zhou L–c, Pan M–h, Yang Z–q. Research Progress of Amodiaquine as an Antimalarial Drug. *Chinese Journal of Parasitology and Parasitic Diseases* 2022; **40**(**6**): 786.

2 Malaria RB. *World Malaria Report 2005*; World Health Organization and UNICEF: Geneva, Switzerland, 2005.

3 Tuteja R. Malaria− an Overview. *The FEBS journal* 2007; **274**(**18**): 4670–4679.

4 Reiter P. Global Warming and Malaria: Knowing the Horse Before Hitching the Cart. *Malaria journal* 2008; **7**: 1–9.

5 Jiang H, Zeng X, Chen Y. Determination of Artesunate in Artesunate and Amodiaquine Hydrochloride Tablets by HPLC. *Chinese Journal of Biochemical Pharmaceutics* 2015; 166–168.

6 Staedke SG, Kamya MR, Dorsey G, Gasasira A, Ndeezi G, Charlebois ED, Rosenthal PJ. Amodiaquine, Sulfadoxine/Pyrimethamine, and Combination Therapy for Treatment of Uncomplicated Falciparum Malaria in Kampala, Uganda: a Randomised Trial. *The Lancet* 2001; **358**(**9279**): 368–374.

7 Sun G, Zhan T, Owusu BG, Daniel A－M, Liu G, Jiang W. Revised Reinforcement Learning Based on Anchor Graph Hashing for Autonomous Cell Activation in Cloud－RANs. *Future Generation Computer Systems* 2020; **104**: 60–73.

8 Li S, Singh K, Riedel N, Yu F, Jahnke I. Digital Learning Experience Design and Research of a Self–Paced Online Course for Risk–Based Inspection of Food Imports. *Food Control* 2022; **135**: 108698.

9 Yu F, Milord J, Orton S, Flores L, Marra R. Students' Evaluation Toward Online Teaching Strategies for

Engineering Courses during COVID. In Proceedings of the 2021 ASEE Midwest Section Conference, Virtual Conference, 13–15 September 2021.

10 Shen Y, Gu H – M, Qin S, Zhang D – W. Surf4, Cargo Trafficking, Lipid Metabolism, and Therapeutic Implications. *Journal of Molecular Cell Biology* 2022; **14**(**9**): mjac063.

11 Shen Y, Wang B, Deng S, Zhai L, Gu H-M, Alabi A, Xia X, Zhao Y, Chang X, Qin S, Zhang D-W. Surf4 Regulates Expression of Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) but Is Not Required for PCSK9 Secretion in Cultured Human Hepatocytes. *Biochimica et Biophysica Acta (BBA) – Molecular and Cell Biology of Lipids* 2020; **1865**(**2**): 158555.

12 Xia D, Alexander AK, Isbell A, Zhang S, Ou J, Liu XM. Establishing a Co–Culture System for Clostridium Cellulovorans and Clostridium Aceticum for High Efficiency Biomass Transformation. *J Sci Heal Univ Ala* 2017; **14**: 8–13.

13 Wang B, Shen Y, Zhai L, Xia X, Gu H-M, Wang M, Zhao Y, Chang X, Alabi A, Xing S, Deng S, Liu B, Wang G, Qin S, Zhang D-W. Atherosclerosis – Associated Hepatic Secretion of VLDL but Not PCSK9 Is Dependent on Cargo Receptor Protein Surf4. *Journal of Lipid Research* 2021; **62**: 100091.

14 Wang M, Alabi A, Gu H – M, Gill G, Zhang Z, Jarad S, Xia X – D, Shen Y, Wang G – Q, Zhang D – W. Identification of Amino Acid Residues in the MT–Loop of MT1–MMP Critical for Its Ability to Cleave Low –Density Lipoprotein Receptor. *Frontiers in Cardiovascular Medicine* 2022; **9**: 917238..

15 Mock MB, Zhang S, Pniak B, Belt N, Witherspoon M, Summers RM. Substrate Promiscuity of the NdmCDE N7–Demethylase Enzyme Complex. *Biotechnology Notes* 2021; **2**: 18–25.

16 Liu Y, Liu L, Yang L, Hao L, Bao Y. Measuring Distance Using Ultra – Wideband Radio Technology Enhanced by Extreme Gradient Boosting Decision Tree (XGBoost). *Automation in Construction* 2021; **126**: 103678.

17 Deng X, Kawano Y. Terahertz Plasmonics and Nano – Carbon Electronics for Nano – Micro Sensing and Imaging. *International Journal of Automation Technology* 2018; **12**(**1**): 87–96.

18 Qiu Y. *Estimation of Tail Risk Measures in Finance: Approaches to Extreme Value Mixture Modeling*; Johns Hopkins University: Baltimore, MD, USA, 2019.

19 Horne J, Beddingfield E, Knapp M, Mitchell S, Crawford L, Mills SB, Wrist A, Zhang S, Summers RM. Caffeine and Theophylline Inhibit β–Galactosidase Activity and Reduce Expression in Escherichia coli. *ACS Omega* 2020; **5**(**50**): 32250–32255..

20 Chen F, Luo Z. Learning Robust Heterogeneous Signal Features from Parallel Neural Network for Audio Sentiment Analysis. 2018. arXiv:1811.08065.

21 Chen F, Luo Z. Sentiment Analysis Using Deep Robust Complementary Fusion of Multi–Features and Multi –Modalities. 2019. CoRR abs/1904.08138.

22 Luo Z, Xu H, Chen F. Audio Sentiment Analysis by Heterogeneous Signal Features Learned from Utterance – Based Parallel Neural Network. In Proceedings of the AffCon@ AAAI 2019, Honolulu, HI, USA, 27 January 2019.

23 Liu Y, Bao Y. Review on Automated Condition Assessment of Pipelines with Machine Learning. *Advanced Engineering Informatics* 2022; **53**: 101687.

24 Deng X, Kawano Y. Surface Plasmon Polariton Graphene Midinfrared Photodetector with Multifrequency Resonance. *Journal of Nanophotonics* 2018; **12**(**2**): 026017–026017.

25 Deng X, Dong Z, Ma X, Wu H, Wang B, Du X. Exploration on Mechanics Design for Scanning Tunneling Microscope. In Proceedings of the 2009 Symposium on Photonics and Optoelectronics, Wuhan, China, 14–16 August 2009.

26 Luo Z, Zeng X, Bao Z, Xu M. Deep Learning – Based Strategy for Macromolecules Classification with Imbalanced Data from Cellular Electron Cryotomography. In Proceedings of the 2019 International Joint Conference on Neural Networks (IJCNN), Budapest, Hungary, 14–19 July 2019.

27 Luo Z, Xu H, Chen F. Utterance-Based Audio Sentiment Analysis Learned by a Parallel Combination of CNN and LSTM. 2018. arXiv:1811.08065.

28 Chen F, Luo Z, Xu Y, Ke D. Complementary Fusion of Multi–Features and Multi–Modalities in Sentiment

Analysis. 2019. arXiv*:*1904.08138.

29 Rahman K, Khan SU, Fahad S, Chang MX, Abbas A, Khan WU, Rahman L, Haq ZU, Nabi G, Khan D. Nano – Biotechnology: a New Approach to Treat and Prevent Malaria. *International Journal of Nanomedicine* 2019; **14**: 401–1410.

30 Yabré M, Ferey L, Somé TI, Sivadier G, Gaudin K. Development of a Green HPLC Method for the Analysis of Artesunate and Amodiaquine Impurities Using Quality by Design. *Journal of Pharmaceutical and Biomedical Analysis* 2020; **190**: 113507.

31 De Joarder D, Sarkar R, Mukhopadhyay C. Sustainable Green Technologies for Synthesis of Potential Drugs Targeted Toward Tropical Diseases. In *Green Approaches in Medicinal Chemistry for Sustainable Drug Design*; Elsevier: Amsterdam, The Netherlands, 2020.

32 Verdaguer IB, Crispim M, Zafra C A, Sussmann RAC, Buriticá NL, Melo HR, Azevedo MF, Almeida FG, Kimura EA, Katzin AM. Exploring Ubiquinone Biosynthesis Inhibition as a Strategy for Improving Atovaquone Efficacy in Malaria. *Antimicrobial Agents and Chemotherapy* 2021; **65**(**4**): e01516–20.

33 Abacha YZ, Abacha YZ, Forkuo AD, Gbedema SY, Mittal N, Ottilie S, Rocamora F, Winzeler E, van Schalkwyk DA, Kelly JM, Taylor MC, Reader J, Birkholtz L-M, Lisgarten DR, Cockcroft JK, Lisgarten JN, Palmer RA, Talbert RC, Shnyder SD, Wright CW. Semi–Synthetic Analogues of Cryptolepine as a Potential Source of Sustainable Drugs for the Treatment of Malaria, Human African Trypanosomiasis, and Cancer. *Frontiers in Pharmacology* 2022;**13**: 875647.

34 Krampa FD, Aniweh Y, Kanyong P, Awandare GA. Recent Advances in the Development of Biosensors for Malaria Diagnosis. *Sensors* 2020; **20**(**3**): 799.

35 Yu F, Milord JO, Flores LY, Marra R. Work in Progress: Faculty Choice and Reflection on Teaching Strategies to Improve Engineering Self–Efficacy. In Proceedings of the 2022 ASEE Annual Conference, Minneapolis, MN, USA, 26–29 June 2022.

36 Belete TM. Recent Progress in the Development of New Antimalarial Drugs with Novel Targets. *Drug Design, Development and Therapy* 2020; **14**: 3875–3889.

37 Sherman JD. The Green Print: Advancement of Environmental Sustainability in Healthcare. *Resources Conservation and Recycling* 2020; **161**: 104882.